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# (54) PREPARATION OF (THREO)-1-ARYL-2-ACYLAMIDO-3-FLUORO-1-PROPANOLS.

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**Descripti n**

Background of the Invention

This invention relates to *cis*-1-Aryl-2-(fluoromethyl)oxiranes, and to a method of preparing such compounds.

This invention also relates to a method of preparing (threo)-1-Aryl-2-acylamido-3-fluoro-1-propanols from *cis*-1-Aryl-2-(fluoromethyl)oxiranes. More particularly, this invention relates to preparing D-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanol antibacterial agents, including 3-fluoro-3-deoxy derivatives of chloramphenicol and of thiamphenicol.

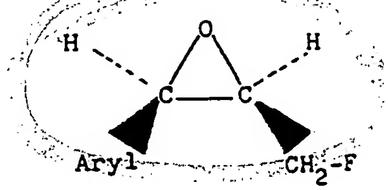
D-(threo)-1-Aryl(phenyl or para- and/or meta-substituted phenyl)-2-acylamido-3-fluoro-1-propanols and racemic mixtures thereof are known in the art as broad spectrum antibacterial agents useful in the treatment of gram positive, gram negative and rickettsial infections. See, for example, U.S. Patent No. 4,235,892, and 4,361,557.

DD—A—83,161 is directed to a process for preparing N-derivatives of D-(−)-*trans*-1-p-nitrophenyl-2-amino-propandiol-(1,3), e.g. choramphenicol and azidoamphenicol by reacting dichloroacetamide or azido-acetamide with *trans*-1-p-nitrophenyl-propanol-(3)-epoxide-(1,2). This reference does not disclose or suggest the racemic mixture of cis-1-aryl-2-(fluoromethyl) oxiranes of the present invention or the use of such compounds in preparing D,L-(threo)-1-aryl-2-acrylamido-3-fluoro-1-propanol compounds.

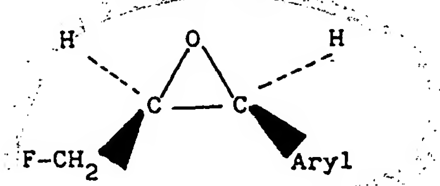
U.S. Patent No. 4,311,857 discloses methods of preparing D-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanols by reaction of D-(threo)-1-Aryl-2-N-protected-amino-1,3-propanediol with dialkylaminosulfur trifluoride followed by removal of the N-protecting group and thence reaction of the resulting D-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol with a lower alkanoic acid derivative. However, the method uses an optically active starting material and it would be economically desirable to provide a synthetic pathway to (threo)-1-Aryl-2-acylamido-3-fluoro-1-propanols employing racemic starting materials and delay a resolution of the racemic mixture to a late step in the process.

Summary of the Invention

The present invention provides a process for the preparation of compounds represented by formulas IVa and IVb

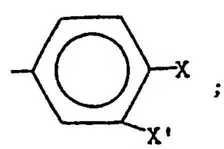


IVa



IVb

wherein Aryl is



and wherein each of X and X' is independently $NO_2$, $SO_2R_1$, $SO_2NH_2$, $SO_2NHR_1$, $OR_1$, $R_1$, CN, halogen, hydrogen, phenyl or phenyl substituted by 1 to 3 halogens, $NO_2$, $SO_2R_1$ or $OR_1$; and wherein $R_1$ is lower alkyl; which comprises the following steps:

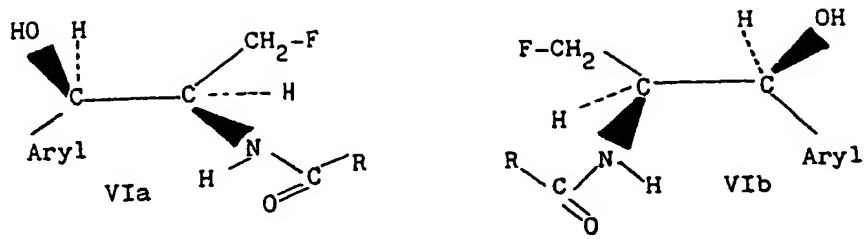
(a) contacting the 3-Aryl-2-propyn-1-ol with a fluorinating agent in an inert organic solvent to form 1-Aryl-3-fluoro-1-propyne;

(b) contacting the product of step (a) with a reagent selective to *cis*-hydrogenation to form a *cis*-1-Aryl-3-fluoro-1-propene; and

(c) contacting the product of step (b) with a peroxyacid to form the compounds represented by the formulas IVa and IVb.

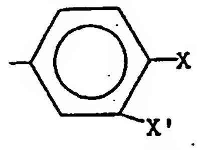
The novel compounds represented by formulas IVa and IVb are *cis*-1-Aryl-2-(fluoromethyl)oxiranes, useful as intermediates in the preparation of D,L-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanols.

The present invention also provides a process for the preparation of D,L-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanols represented by formulas VIa and VIb



VIa VIb

wherein R is lower alkyl or a halogenated derivative thereof; dihalogenodeuteriomethyl, 1-halogeno-1-deuterioethyl; 1-2-dihalogeno-1-deuterioethyl; azidomethyl; or methylsulfonylmethyl; wherein Aryl is



;

wherein each of X and X' is independently $NO_2$, $SO_2R_1$, $SO_2NH_2$, $SO_2NHR_1$, $OR_1$, $R_1$, CN, halogen, hydrogen, phenyl, or phenyl substituted by 1—3 halogens, $NO_2$, $SO_2R_1$, $R_1$, or $OR_1$; and wherein $R_1$ is lower alkyl which comprises the following steps:

(1) converting a *cis*-1-Aryl-2-(fluoromethyl)oxirane into D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol either by (i) contacting the *cis*-1-Aryl-2-(fluoromethyl)oxirane with an alkali metal azide to form D,L-(thero-1-Aryl-2-azido-3-fluoro-1-propanol and then reducing the 2-azido group to a 2-amino group or (ii) contacting the *cis*-1-Aryl-2-(fluoromethyl)oxirane with an imido compound to form a D,L-(threo)-1-Aryl-2-imido-3-fluoro-1-propanol and then converting the 2-imido group to a 2-amino group thereby forming D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanols;

(2) contacting the product of step (1) with a lower alkanoic acid derivative selected from lower alkyl alkanoic acid anhydrides, lower alkyl alkanoyl halide, or a halogeno lower alkyl alkanoic acid halide or anhydride in the presence of a base, or a lower alkyl ester of an α,α-dihalogeno acetic acid or an α,α-dihalogeno propionic acid in a lower alkyl alkanol to produce the compounds of formulas VIa and VIb; and

(3) recovering compounds of formulas VIa and VIb.

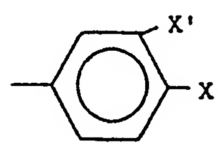
In a preferred embodiment of the present invention the racemic mixture of D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanols, obtained from step (1) of the process is resolved by fractional crystallization of a diastereomeric salt of D-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol and an optically active acid followed by treatment of the diasteriomeric salt with aqueous base and recovery of D-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol, and thence treatment of the D-threo compound with a lower alkanoic acid derivative to form the D-threo enantiomer of the compound of formula VIa.

Detailed Description of the Invention

The term "halogen" as used herein means fluorine, chlorine, bromine or iodine. Fluorine and chlorine are preferred.

The term "lower alkyl" as used herein means straight or branched ($C_1$—$C_6$) alkyl including methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl, iso-hexyl. Methyl and ethyl are preferred.

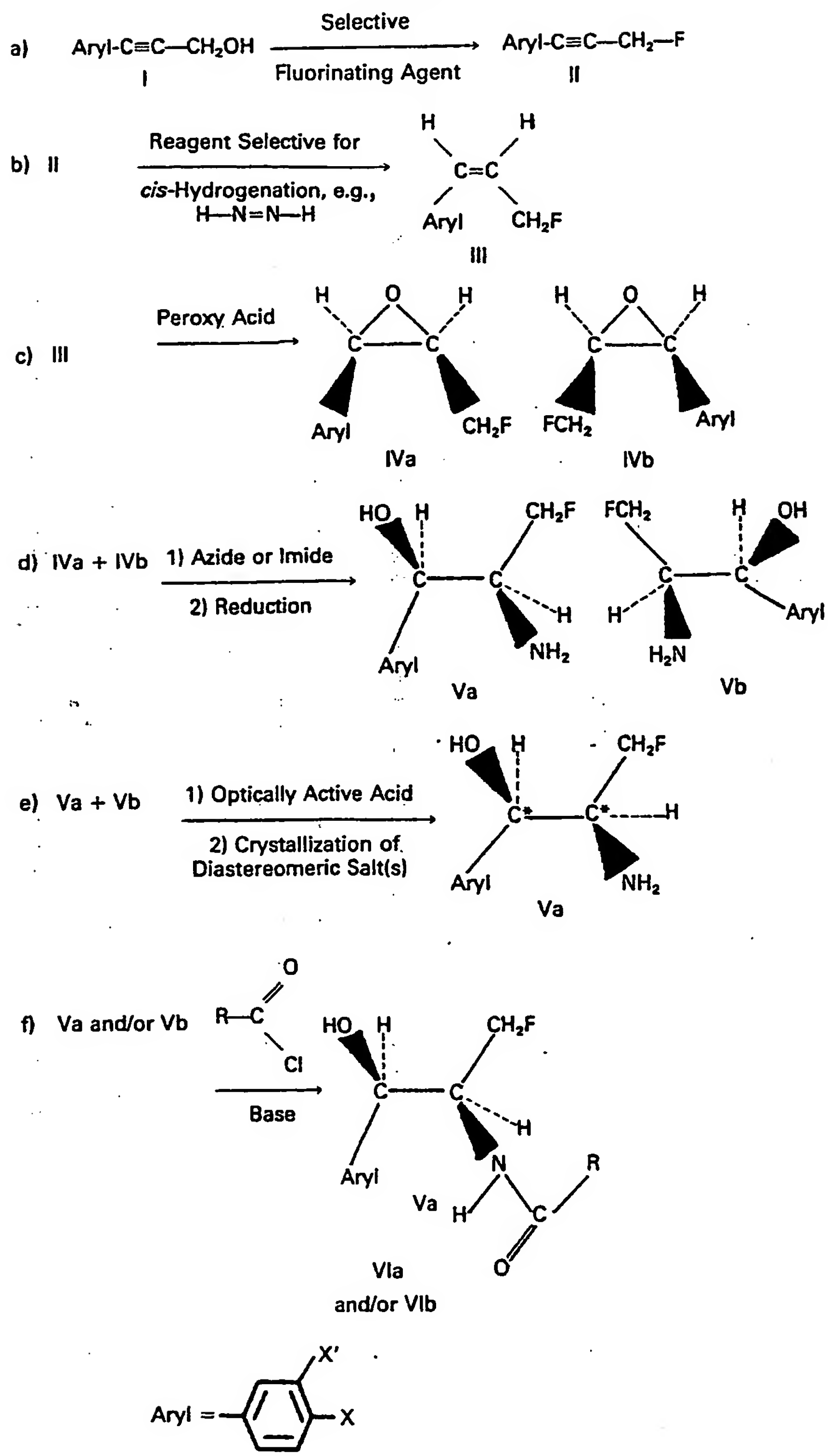
The term "Aryl" as used herein means phenyl or 4-substituted or 3,4-disubstituted phenyl represented by formula



wherein each of X and X' is a member selected from the group consisting of $NO_2$, $SO_2R_1$, $SO_2NH_2$, $SO_2NHR_1$, $OR_1$, $R_1$, CN, halogen, hydrogen, phenyl and phenyl substituted by halogen, $NO_2$, $SO_2CH_3$, $R_1$ or $OR_1$ and wherein $R_1$ is methyl, ethyl, propyl or isopropyl and wherein halogen is fluorine, chlorine or bromine. Particularly interesting Aryl groups are 4-nitrophenyl (X is $NO_2$) and 4-methylsulfonylphenyl (X is $SO_2CH_3$) and 4-sulfonamidophenyl (X = $SO_2NH_2$).

The following Scheme illustrates the multistep process s of this invention for pr paring *cis*-1-Aryl (phenyl or para- and/or meta-substituted phenyl)-(2-fluor methyl)oxiranes and for preparing D,L-(threo) and D-(threo)-1-Aryl(phenyl or para and/or meta substituted phenyl)-2-acylamido-3-fluoro-1-pr panols. The processes comprise a n vel sequence of highly s lective chemical reactions.

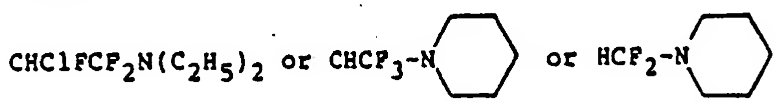
SCHEME



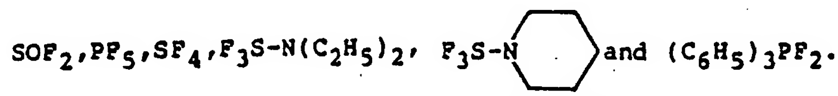

The 3-Aryl-2-propyn-1-ols represented by formula I used as starting materials in step (a) of the processes of the present inv ntion are either known compounds or are conveniently prepar d according to known proc dures. For example, 3-(4-methylsulfonylphenyl)-2-propyn-1-ol is conveniently prepared by

reacting 4-bromophenyl methyl sulfone with propargyl alcohol in the presence of copper(I)iodid bis(triphenylphosphine) palladium(II)chloride and triethylamine. A general exp rim ntal procedure for preparation of 3-Aryl(phenyl or para and/or meta substituted phenyl)-2-propyn-1-ols, such as 3-(4-nitrophenyl)-2-propyn-1-ol is described by M. A. Harris et al. in *J. Chem. Soc.*, Perkin I, pages 1612—1613 (1976).

In step a) of the process depicted in the reaction Scheme, the primary hydroxy moiety in 3-Aryl-2-propyn-1-ol (compound I) is selectively converted into the corresponding primary fluoro moiety (compound 2). Suitable selective fluorinating agents include compounds with two fluorine atoms α to a nitrogen, for example



and compounds having a fluorine atom attached to a hetero atom (e.g. S or P) such as



The preferred fluorinating agent is N-(1,1,2-trifluoro-2-chloroethyl)-N,N-diethylamine, $CHClFCF_2N(C_2H_5)_2$.

The fluorinating step is conveniently carried out at temperatures in the range of about −10° to about +50°C, preferably about 0—30°C in an inert organic solvent. The term "inert organic solvent" means any organic solvent in which compound I and the fluorinating reagents are soluble, and which is essentially inert under the reaction conditions. Dichloromethane is especially preferred.

In step b) of the process depicted in the reaction Scheme, the 1-Aryl-3-fluoro-1-propyne represented by formula II is reduced to the *cis*-1-Aryl-3-fluoro-1-propene represented by formula III by use of a reagent selective for *cis*-hydrogenation such as dimide or hydrogen with a Lindlar catalyst, i.e., palladium precipitated on calcium carbonate and lead (II) oxide selectively poisoned by an aromatic amine, such as quinoline or pyridine in an organic solvent, e.g., ethyl acetate that dissolves at least compound II. Other reagents selective for *cis*-hydrogenation in the process of the present invention include a palladium-on-barium sulfate catalyst poisoned by synthetic quinoline [See D. J. Cram et al., *J. Am. Chem. Soc.*, *78*, 2518 (1956)] or 5% palladium-on-barium sulfate used with pyridine as a solvent [see "Fieser and Fieser's Reagents for Organic Synthesis", Vol. 2, pages 566—569) (1969)]. The particular reagent chosen will depend upon the substituents on the phenyl ring and solubility of the compound represented by formula II as well as the ability of the reagent to effect selective *cis*-hydrogenation of the triple bond with a minimum of side reactions. For the selective *cis*-reduction of the triple bond of 1-(4-methylsulfonylphenyl)-3-fluoro-1-propyne, hydrogen and the Lindlar catalyst selectively poisoned with quinoline are preferred (see H. Lindlar et al. *Org. Syn.*, *46*, 89 (1966)); for the selective *cis*-reduction of the triple bond of 1-(4-nitrophenyl)-3-fluoro-1-propyne, dimide is preferred (see "Fieser and Fieser's Reagents for organic Synthesis", Vol. 8, page 172, Wiley-Interscience, N.Y. 1980). Reaction conditions are not critical; generally, hydrogen pressures of about 1 atmosphere, room temperature and 1—24 hrs. are used.

In step c) of the process depicted in the reaction Scheme, the *cis*-1-Aryl-3-fluoro-1-propene (compound III) is converted into the *cis*-1-Aryl-2-(fluoromethyl)oxiranes (compounds IVa and IVb) by use of an aliphatic or aromatic peroxyacid. Among the suitable aromatic peroxyacids are m-chloroperbenzoic acid, perbenzoic acid, and peroxyphthalic acid. Among the suitable aliphatic peroxyacid acids are peracetic acid and trifluoroperacetic acid. The preferred peroxyacid for step c) is m-chloroperbenzoic acid. Reaction conditions are not critical. Chlorinated solvents, e.g., dichloromethane, reflux temperatures, and reaction times of 10—30 hrs are typically used. See "Fieser and Fieser's Reagents for Organic Synthesis", Vol. 9, pages 108—110.

Compounds IVa and IVb formed in step c are novel compositions of matter and isolated and purified by standard techniques, e.g. extraction, filtration, chromatography and crystallization. The term "Aryl" in *cis*-1-Aryl-2-(fluoromethyl)oxirane is defined hereinabove. Particularly interesting compounds represented by formulas IVa and IVb are *cis*-1-(4-nitrophenyl)-2-(fluoromethyl)oxirane, *cis*-1-(4-sulfonamidophenyl-2-(fluoromethyl)oxirane.

When compounds IVa and IVb are used to produce the D,L- or D-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanols, process steps d + f or d + e + f are performed, respectively. Generally, it is desirable to isolate and purify compounds IVa and IVb after step (c) is performed.

In step d) of the process depicted in the reaction Scheme, the *cis*-1-Aryl-2-(fluoromethyl)oxiranes (compounds IVa and IVb) are selectively converted into a racemic mixture of D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanols (comp unds Va and Vb) by use of nucleophilic nitrogen comp unds in a dry aprotic solvent such as dimethylformamide or dimethyl sulfoxid at elevated temperatur s (90°—120°C) for 10—40 hrs. Typical suitable nucleophilic nitrogen compounds are alkali metal (especially $Na^+$ and $K^+$) imides e.g., potassium salts of phthalimide, 1,8-naphthal n dicarb ximide, 5,6-norbornen dicarboximide or succinimide in combination with the fr e imide in a rati of 1:4 to 0.05:4. The aroyl gr up, e.g., phthaloyl group is

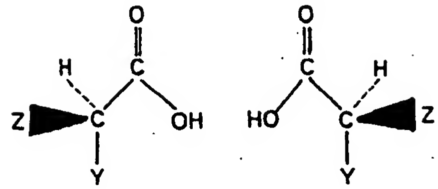
conveniently removed by treatm nt with hydroxylamine hydrochloride and an alkoxid base, e.g., sodium methoxide in methanol to produce the free amine. Other suitable nucleophilic nitrogen compounds include th alkali m tal azides (e.g., $NaN_3$, $KN_3$) preferably buffer d with, for example, ammonium chloride. The azido group is reduced, conveniently with hydrogen in the pres nce of a catalyst, especially with hydrogen and 10% palladium-on-charcoal at atmospheric pressure and at room temperature to give compound Va and Vb containing the free amino group. Use of either alkali metal azides or alkali metal imido compounds in combination with the free imide produces a mixture of compounds which must be purified by, for example, fractional crystallization before conversion to the free amine is effected.

In step f) of the process depicted in the reaction Scheme, D,L- or D-(threo)-1-Aryl-2-amino-3-fluoro-1-propanols (the mixture of compounds Va and/or Vb) is converted into the 2-acylamido derivative compounds VIa and VIb by reaction of compounds Va and/or Vb in the presence of a base and a suitable organic solvent for the reactants with a lower alkyl alkanoic acid derivative or a halogeno lower alkyl alkanoic acid halide (e.g. fluoride, chloride) or anhydride, or with a lower lakyl ester of an α,α-dihalogeno-propionic acid under reflux until the reaction goes to completion, typically in 10—20 hrs. Halogeno acetic or propionic acid chlorides are preferred halogeno lower alkyl alkanoic acid halides. Typically, the base is an aliphatic amine and the organic solvent suitable for the reactants is a lower alkyl alkanol, especially methanol or ethanol or a halogenated alkane, e.g. dichloromethane. Of the lower alkyl alkanoic acid derivatives, acetic and propionic acid, chlorides and acid anhydrides are preferred. Of the lower alkyl esters of the preferred acid derivatives, the methyl and ethyl esters of the dihalogeno acetic acids and the α,α-dihalogenopropionic acids are preferred. Typical of the lower alkyl halogeno alkanoic acid derivatives are halogeno acetic and halogeno propionic acid chlorides or anhydrides, especially those substituted by one, two or three halogens (F, Cl, Br or I) including mono-, di- and trifluoro-, mono-, di- and trichloro- and mono- and dibromo- and mono-iodoacetic acid chlorides or anhydrides or esters as well as the mono- and difluoro-, the mono- and dichloro-, the mono- and dibromo- and the mono-iodopropionic acid chlorides or anhydrides or esters. The halogen substituents in the propionic acid derivatives are preferably on the carbon alpha to the carbonyl function. Other typical suitable alkanoic acid derivatives are the mixed dihalogeno propionic acid derivatives in which both halogens are preferably bonded to the carbon alpha to the carbonyl function, e.g., fluorochloro-, fluorobromo- and chlorobromoacetic acid chlorides or anhydrides or esters as well as α-fluoro-, α-chloro- and α-bromopropionic acid chlorides or anhydrides or esters as well as trihalogenoacetic acid derivatives such as dichlorofluoro- and difluorochloroacetic acid chlorides or anhydrides or esters. Additionally, suitable are those halogeno acetic and halogeno propionic acid chlorides and anhydrides and esters having a deuterio atom on the carbon alpha to the carbonyl function, e.g., dihalogenodeuterioacetic acid chlorides or anhydrides such as dichlorodeuterio difluoro-deuterio- and chlorofluorodeuterioacetic acid chlorides or anhydrides or esters, as well as α,α-difluoro-α-deuterio-, α-fluoro-α-deuterio- and α,α-dichloro-α-deuteriopropionic acid chlorides, anhydrides or esters. Of the foregoing, dichloroacetic, difluoroacetic, fluorochloroacetic acid chlorides, anhydrides and the methyl and ethyl esters as well as deuterio derivatives thereof are preferred.

The racemic mixture of compounds Va and Vb resulting from step d) of Scheme detailed above has antifungal activity. However, the preferred biologically active D-(threo)-enantiomer, compound Va, can be separated from the racemic mixture by a variety of techniques known to those skilled in the art, but preferably by fractional crystallization of the diastereomeric ammonium carboxylate salt of the D-(threo) enantiomer with an optically active acid.

The resolution step of the preferred embodiment of the process of the present invention is performed on the racemic mixture of D,L-(threo)-1-Aryl-1-2-amino-3-fluoro-1-propanols (compounds Va and Vb) prior to the step f) of the process depicted in the reaction Scheme. The racemic mixture of compounds represented by formulas Va and Vb is contacted with an optically active acid, one enantiomer of which forms a crystalline diastereomeric salt with the D-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol (compound Va), said salt having a higher melting point, and/or a lower solubility and/or higher crystallizability compared to that for the L-threo enantiomer. As is well known to those skilled in the art, it is advantageous to explore, on a millimole scale, the salt forming properties i.e., melting point, solubility and crystallinity of optically active acids described in the literature in order to select the optimal resolving agent available as well as to provide crystalline diastereomeric salts which can be used as seed crystals in resolving the racemic D,L-threo aminofluoro propanol. Generally, as is well known in the art, a resolution through separation by crystallization of diastereomeric salts is most likely to succeed without difficulty when the acid and basic salt-forming centers of both components are proximate in space to those factors which render each asymmetric.

Typical suitable optically active acids useful for successful resolution of the racemic D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanols are those acids represented by the formulas A and B



A B

wherein Z is a bulky alkyl or aromatic group such as phenyl, naphthyl, ($C_4$—$C_{10}$) branched alkyl (e.g. isobutyl, neopentyl, isohexyl, isooctyl and the like) and wherein Y is a polar group such as

$$-OR_2,\ NH-\overset{O}{\overset{\|}{C}}-R_2 \text{ or } O-\overset{O}{\overset{\|}{C}}R_2 \text{ or } O-\overset{O}{\overset{\|}{C}}-Ar$$

wherein $R_2$ is straight or branched ($C_1$—$C_6$)alkyl, for example, methyl, ethyl, propyls, butyls, pentyls, hexyls and wherein Ar is phenyl or para- or meta-substituted phenyl. Suitable Y groups include

$$CH_3O-, C_2H_5O-, C_4H_9O-, C_6H_{13}O- \ CH_3\overset{O}{\overset{\|}{C}}NH-, C_6H_5\overset{O}{\overset{\|}{C}}-, CH_3\overset{O}{\overset{\|}{C}}-O-\text{and } C_4H_9\overset{O}{\overset{\|}{C}}-.$$

O-(+)-(S)-O-methylmandelic acid (formula A wherein Y = $OCH_3$ and Z = $C_6H_5$) is especially preferred.

Generally, no more than about an equivalent of the optically active acid is heated (steam bath) with the racemic D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanols in a suitable organic solvent. The resolution is improved by seeding of the solution of racemate and optically active acid with the authentic neutral diastereomeric salt of the desired D-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol and the optimal optically active acid and thereafter stirring the mixture for a short time (2 hrs). The optical rotation and optical purities of the isolated salt and the free amine are determined and the diastereomeric salt is repeatedly recrystallized to constant optical purity. When the solution of the diastereomeric salt of D-threo-1-(4-methylsulfonylphenyl)-2-amino-3-fluoro-1-propanol (compound Va wherein Aryl = 4-$CH_3SO_2C_6H_4$—) and (+)-S-O-methylmandelic acid was seeded with the authentic diastereomeric salt and stirred, the isolated salt had an optical purity of aboput 96% and was obtained in about 46% yield after two crystallization from n-butanol.

Among the suitable organic solvents are acetone, ethanol, ethanol-ether (1:1, v/v) and n-butanol. Use of n-butanol gave the best results (high yield and optical purity of diastereomeric salt isolated) and is preferred. The 1:1 ethanol-ether mixture gave a diastereomeric salt with an optical purity comparable to that using n-butanol, hoowever, in lower yield.

Compound Va can be conveniently isolated as the free amine from an aqueous solution of the diastereomeric salt by treatment of the diastereomeric salt with aqueous base, e.g., alkali metal hydroxide or carbonate and extraction of Va with an immiscible organic solvent.

## Examples

### General Experimental

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared (ir) spectra were recorded with a Perkin-Elmer 598 spectrophotometer. The H NMR spectra were recorded with a Bruker CXP—2;; (200 MHz) or a Varian-T-60 (60 MHz) spectrometer with tetramethylsilane (TMS) as the internal standard; chemical shifts are given in parts per million down field from TMS. Optical rotations were measured with a Perkin-Elmer model 141 automatic polarimeter. Thin-layer chromatography (tlc) was performed using precoated thin-layer chromatography plates (kieselgel 60, $F_{254}$, E. Merck) with a fluorescence indicator in the following solvent syhstems (v/v): (*A*) ethyl acetate-hexane (1:1); (*B*) ethyl acetate-hexane (3:1). Compounds were located by ultraviolet light. Preparative thin-layer chromatography was performed using pre-coated thin-layer chromatography plates (silica gel GF, Analtech). Column chromatography was performed on silica gel 60 (70—230 mesh, E. Merck). Temperatures are in degrees Celsius.

## Exampl 1

### 1-(4-Methylsulfonylphenyl)-3-Fluoro-1-Propyn

T a stirred soluti n f *N*-(1,1,2-trifluor -2-chl ro thyl)-N,N-diethylamine (6.2 g 32.5 mmol) in $CH_2Cl_2$ (20 mL) at 0—5°, add 3-4-methylsulfonylphenyl)-2-propyn-1-ol (4.78 g; 22.8 mm l) in $CH_2Cl_2$ (15 mL) ver 10—15 min. Treat the solution with $CF_3CO_2H$ (0.2 mL) and maintain the treated solution at 20—25° for 20 hrs.

Add methanol (5 mL) and partition the mixture in $CH_2Cl_2$—$H_2O$. Stir the organic phase 1 hr with methanol (10 mL) and anhydrous $Na_2CO_3$ (10 g) [to hydrolyze any esters], filter and evap rate the organic phase. Filter the residue dissolved in $CH_2Cl_2$ through ~20 g f silica g l and elute with $CH_2Cl_2$. Evaporate all product-containing-fractions and dissolve th residue

$$(\text{product} + \text{CHClF}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{N}(\text{C}_2\text{H}_5)_2$$

in ether (15 mL) and dilute the solution so formed slowly with hexanes (75 mL). Refrigerate the solution and collect the product by filtration. Wash the filtered product with hexanes and dry the washed product at 25° in high vacuum to give fine white needles of the title compound, mp 97—99° (3.25 g; 68% of theory). $^1$H NMR ($CDCl_3$) δ: 3.06 (s, 3H), 5.20 (d, J = 47, 2H), 7.64 (d, J = 8, 2H) and 7.95 (d, J = 8, 2H).

## Example 2

cis-1-(4-Methylsulfonylphenyl)-3-Fluoro-2-Propene

(A) *cis-hydrogenation using Lindlar catalyst and pyridine:* Stir a mixture of 533 mg, 2.51 mmoles of the title compound of Example 1 (recrystallized from dichloromethane-hexane), 211 mg, 2.67 mmoles of pyridine and 127 mg of Lindlar catalyst (palladium on calcium carbonate, poisoned with lead (obtained from Aldrich) in 25 mL of ethyl acetate under hydrogen at atmospheric pressure at 26°C for 1 hr until the theoretical amount of hydrogen (62 mL) is consumed. Remove the catalyst by filtration and wash it with ethyl acetate. Wash the ethyl acetate solution successively with ice-col 4% HCl over anhydrous $MgSO_4$. Evaporate solvent under vacuum to give the title compound as an oil (534 mg).

(B) *cis-hydrogenation using Lindlar catalyst and quinoline:* Shake a mixture of recrystallized title compound of Example 1 (1 g, 4.72 mmoles), quinoline (60 mg, 99% pure Aldrich) and Lindlar catalyst of procedure A of Example 2 (200 mg) in ethyl acetate (50 mL) in a Parr apparatus under hydrogen at atmospheric pressure at 30° for 20 min. or until theoretical amount of hydrogen (118 mL) is taken up. Remove catalyst by filtration and wash it with ethyl acetate. Evaporate the solvent under vacuum at 35° to give an oil. Dissolve the oil in dichloromethane (40 mL) and wash the dichloromethane solution successively with ice-cold 1*M* HCl solution, saturated $NaHCO_3$ solution and water, and then dry over anhydrous $MgSO_4$. Evaporate the under vacuum to give the title compound as an oil (1 g). Purify a portion of the oil (220 mg) by column chromatography. Elute the column with ethyl acetate-hexane (1:1, v/v) to give the title compound as an oil (213 mg). The oil was 95% pure and contained 5% of the over-reduced compound 3-(4-methylsulfonylphenyl)-1-fluoropropane and had the following physical and spectral properties:

$R_f$ = 0.44 (solvent *A*); $\nu_{max}$ (film): 2990, 1580 (C=C) cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 3.06 (s, 3H), 5.06 (ddd, 2H, $J_{3'F}$ = 46.6 Hz, $J_{3,3'}$ = 6.4 Hz, $J_{3,2}$ = $J_{3',2}$ = 1.3 Hz), 6.06 (m, 1H, $J_{2,F}$ = 17.3 Hz, $J_{1,2}$ = 12.3 Hz, $J_{2,3'}$ = $J_{2,3}$ = 1.3 Hz), 6.70 (bd, 1H, $J_{1,2}$ = 12.3 Hz), 7.31 (d, 2H, J = 8.3 Hz), 7.85 (d, 2H, J = 8.1 Hz).

## Example 3

cis-1-(4-Methylsulfonylphenyl)-2-(fluoromethyl)oxirane

A. Reflux a solution of the title compound of Example 2 (533 mg, 2.49 mmoles), *m*-chloroperbenzoic acid (m-CPBA) (863 mg, 5.00 mmoles) and 3-*tert*-butyl-4-hydroxy-5-methylphenylsulfide (an inhibitor, 30 mg, Aldrich) in dry dichloromethane (20 mL) ($P_2O_5$ dried) for 17 hrs. Add another portion of *m*-CPBA (400 mg) and reflux the solution for an additional 5 hrs. Cool the solution to room temperature, and wash the cooled solution with saturated sodium bicarbonate solution (20 mL) and add thereto sodium sulfite ($Na_2SO_3$, 3 g). Stir the resulting mixture for 30 min. Separate the organic layer and extract the aqueous layer with dichloromethane (20 mL). Wash the combined organic extract with water and dry over anhydrous $MgSO_4$. Evaporate the solvent under vacuum to give a syrup. Chromatograph the syrup on two preparative tlc plates using ethyl acetate-hexane (1:1 v/v). Extract the bands containing the product with ethyl acetate to give the title compound, a solid (473 mg, 83% of theory). Recrystallized the solid from dichloromethane-ether; m.p. 91—93°C, $R_f$ = 0.33 (solvent *A*); $\nu_{max}$ (KBr): 3000, 1596 (C=C) cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 3.07 (s, 3H), 3.63 (m, 1H, $J_{2,F}$ = 7.6 Hz, $J_{2,1}$ = 4.2 Hz, $J_{2,3}$ = 4.7 Hz, $J_{2,3'}$ = 6.4 Hz), 4.22 (ddd, 1H, $J_{3,F}$ = 47.5 Hz, $J_{3,3'}$ = 10.6 Hz, $J_{3,2}$ = 6.4 Hz), 4.30 (dd, 1H, $J_{1,2}$ = 4.2 Hz, $J_{1,F}$ = 2.1 Hz), 4.33 (ddd, 1H, $J_{3',F}$ = 46.8 Hz, $J_{3',3}$ = 10.6 Hz, $J_{3',2}$ = 4.7 Hz), 6.87 (d, 2H, J = 8.1 Hz), 7.96 (d, 2H, J = 8.7 Hz).

B. More conveniently, isolate the title compound (2.78 g, 68%) by direct crystallization from dichloromethaneether of the reaction mixture from the m-CPBA peroxidation of 3.84 g of the *cis*-1-(4-Methylsulfonylphenyl)-3-fluoro-2-propene.

## Exampl 4

D,L-(*threo*)-1-(4-Methylsulfonylphenyl)-2-Phthalimido-3-Fluoro-1-Pr panol

A. *Reaction of the title compound of Example 3 with potassium phthalimide and phthalimide.*

Heat a mixture of th title compound of Exampl 3 (500 mg, 2.17 mmoles), and fin ly powdered potas-

sium phthalimide (400 mg, 2.16 mmoles) and phthalimide (1.278 g, 8.69 mmoles) in dry DMF (dried over $P_2O_5$ and distilled under reduced pressure) with stirring in an oil bath under nitrogen at 93—97° for 24 hrs. Cool the reaction mixture to room temperatur and p ur the cooled mixture into ice-cooled 0.1*M* HCl (100 mL) and extract twice with dichloromethane (30 mL). Wash the combined extract successively with saturated sodium bicarbonate (30 mL) and water and then dry over anhydrous $Na_2SO_4$. Evaporate the solvent under vacuum to give a solid residue, and treat the solid with ethyl acetate-hexanes (1:1, v/v). Remove the precipitated solid by filtration and wash it with ethyl acetate-hexanes (10:1, v/v) (600 mg of phthalimide). Concentrate the filtrate and remove the precipitated solid as described above. Dissolve the residue in DMSO (1 mL) and apply the solution onto a column of silica gel (100 g). Elute the column with ethyl acetate-hexanes (3:2, v/v). Evaporate the solvent to give a solid (438 mg), and treat the solid with isopropyl alcohol. Remove the solid by filtration and wash it with isopropyl alcohol (yield 220 mg, 26.8%). Recrystallize the compound from isopropyl alcohol to give the title compound, colorless plates, m.p. 185—187° (cf. *D*-(threo) isomer gave white needles from isopropyl alcohol; m.p. 175—177°C), $R_f$ = 0.027 (solvent *B*); $\nu_{max}$ (KBr): 3340 (OH), 1752 (symmetric C=O), 1685 (asymmetric C=O), 1587 (C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$-DMSO-$d_6$, 4:1, v/v) δ: 3.07 (s, 3H), 4.33 (ddd, 1H, $J_{3,F}$ = 44.9 Hz, $J_{3,3'}$ = 8.9 Hz, $J_{3,2}$ = 4.0 Hz), 4.67 (m, 1H, $J_{2,F}$ = 16.5 Hz, $J_{2,3}$ = 4.0 Hz, $J_{2,3'}$ = 8.9 Hz, $J_{2,1}$ = 8.3 Hz), 4.85 (dt, 1H, $J_{3',F}$ = 45.8 Hz, $J_{3,3'}$ = $J_{3,2}$ = 8.9 Hz), 5.30 (d, 1H, $J_{1,2}$ = 8.3 Hz), 5.83 (OH) (bs, 1H), 7.64 (d, 2H, J = 8.5 Hz), 7.76 (m, 4H), 7.88 (d, J = 8.5 Hz).

B. *Reaction of the title compound of Example 3 with anhydrous potassium fluoride and phthalimide*

Stir a mixture of the title compound of Example 3 and phthalimide (364 mg, 2.48 mmoles), and anhydrous potassium fluoride (Aldrich, 556 mg) in dry DMF (4 mL) at 90° in an oil bath for 35 hrs. Cool the reaction mixture to room temperature and dilute with dichloromethane. Pour the reaction mixture into water and separate the organic layer. Extract the aqueous layer with dichloromethane (10 mL). Wash the combined extracts with water and dry over anhydrous magnesium sulfate. Evaporate the solvent under vacuum give a solid, and treat the solid with ethyl acetate. Remove the solid by filtration and wash the solid with ethyl acetate. Evaporate the filtrate under vacuum to give a semisolid residue. Dissolve the residue in DMSO (1 mL) and apply the solution onto a column of silica gel (46 g). Elute the column with the ethyl acetate-hexanes (3:2, v/v). Evaporate the eluant and isolate four compounds: phthalimide, unreacted starting material (26.0 mg), unknown component A (24.6 mg), and component B (104 mg). The component B contained two to three compounds including the title compound (50%). Dissolve a portion (80 mg) of this mixture (compound B) in hot isopropyl alcohol (3 mL) and cool the solution to room temperature and thence to 0°. A crystalline solid was removed by filtration and washed with cold isopropyl alcohol (22 mg, 15%). The compound had m.p., and ir and $^1H$ NMR spectra, identical to those, respectively, of the title compound obtained in procedure (A) of Example 4.

Example 5

D,L-(*threo*)-1-(4-Methylsulfonylphenyl)-2-Amino-3-Fluoro-1-Propanol

Dissolve hydroxylamine hydrochloride (460 mg) in dry methanol (25 mL) (dried with Mg) with stirring. Add solid sodium methoxide (575 mg) to the resulting solution and stir the mixture for 0.5 hr. Remove the precipitated solid by suction filtration. To the clear filtrate, add the title compound of Example 4 (500 mg, 1.32 mmoles). Stir the mixture for 19 hrs. at room temperature. Evaporate the solvent under vacuum and stir the resulting syrupy residue with an ice-cooled mixture of chloroform (10 mL), 30% NaOH solution (10 mL) and methanol (2 mL) until the residue completely dissolves. Separate the organic layer and extract the aqueous layer with chloroform (5 × 10 mL). Dry the combined chloroform extracts over anhydrous $Na_2SO_4$ and evaporate the solvent under vacuum to give a syrup which crystallized spontaneously (yield 381 mg, 97%). Recrystallize from methanol to give the title compound, white crystals; m.p. 143—144°; $R_f$ = 0.22 (solvent *C*); $\nu_{max}$ (KBr): 3330 and 3270 ($NH_2$), 3040 (OH), 1581 ($NH_2$) $cm^{-1}$; $^1H$ NMR ($CDCl_3$-DMSO-$d_6$, 2:1, v/v) δ: 1.46 ($NH_2$) (bs, 2H), 2.97—3.12 (m, 1H), 3.07 (s, 3H), 4.18 (ddd, 1H, $J_{3,F}$ = 34.2 Hz, $J_{3,3'}$ = 9.0 Hz, $J_{3,2}$ = 5.9 Hz), 4.41 (ddd, 1H, $J_{3',F}$ = 34.2 Hz, $J_{3',3}$ = 9 Hz, $J_{3',2}$ = 5.9 Hz), 4.71 (d, 1H, $J_{1,2}$ = 4.2 Hz), 5.53 (OH) (bs, 1H), 7.53 (d, 2H, J = 8.1 Hz), 7.80 (d, 2H, J = 8.1 Hz).

Example 6

D,L-(*threo*)-1-(4-Methylsulfonylphenyl-2-Azido-3-Fluoro-1-Propanol

Heat a mixture of the title compound of Example 3 (500 mg, 2.17 mmoles), sodium azide (565 mg), and ammonium chloride (465 mg) in dry DMSO (10 mL), with stirring, in an oil bath at 70° for 12 hrs. Pour the resulting reaction mixture into ice water and extract twice with dichloromethane (30 mL × 2). Wash the combined extracts with water twice and dry the washed extracts over anhydrous sodium sulfate. Evaporate the solvent to give a syrup (491 mg) and dissolve the resulting syrup with a small amount of dichloromethane. Add ether to the resulting solution. Collect a crystalline solid by filtration and wash it with ether to give the title compound (yi ld 164 mg, 27.6%). m.p. 121—123°; $R_f$ = 0.33 (solvent *B*); $\nu_{max}$ (KBr): 3430 (OH), 2990, 2080 ($N_3$), 1585 (C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$-DMSO-$d_6$, 4:1, v/v) δ: 3.07 (s, 3H), 3.75 (m, 1H, $J_{2,1}$ = 5.2 Hz, $J_{2,3}$ = 6.8 Hz, $J_{2,3'}$ = 3.6 Hz, $J_{2,F}$ = 18.2 Hz), 4.31 (ddd, 1H, $J_{3,F}$ = 47.5 Hz, $J_{3,2}$ = 6.8 Hz, $J_{3,3'}$ = 10.0 Hz), 4.61 (ddd, 1H, $J_{3',F}$ = 45.3 Hz, $J_{3',2}$ = 3.6 Hz, $J_{3,3'}$ = 10.0 Hz), 4.90 (t, 1H, $J_{1,2}$ = $J_1$,OH = 5.2 Hz), 5.94 (OH) (d, 1H, $J_{OH,1}$ = 5.2 Hz), 7.59 (d, 2H, J = 8.1 Hz), 7.85 (d, 2H, J = 8.1 Hz).

Example 7

D,L-(*threo*)-1-(4-Methylsulfonylphenyl)-2-Amin -3-Fluoro-1-Propanol

Dissolve the title compound of Example 6 (100 mg) in methanol (25 mL) and add 10% palladium-on-charcoal (16 mg) in methan l (2—3 mL) to the solution. Shake the resulting mixture in a Parr apparatus under hydrogen at atmospheric pressure at room temperature for 1.5 hr. Remove catalyst by filtration and wash same with methanol. Evaporate solvent under vacuum to afford the title compound as a syrup (~90 mg). The compound was essentially homogeneous on tlc, and was used in Example 8B without purification.

Example 8

D,L-(*threo*)-1-(4-Methylsulfonylphenyl)-2-Dichloro-Acetamido-3-Fluoro-1-Propanol

A. Dissolve the title compound of Example 5 (208 mg, 0.841 mmoles) in methyl dichloroacetate (4 mL), triethylamine (0.1 mL) and dry methanol (1.6 mL). Reflux the resulting solution for 11 hrs. under nitrogen. Evaporate solvent under vacuum (0.5 mmHg) to give a syrup. Dissolve the syrup in dichloromethane and apply the resulting solution on to a column of silica gel (45 g). Elute the column with ethyl acetate-hexanes (4:1, v/v) to give a solid 22 mg, 82%). Recrystallize the solid from a small amount of isopropyl alcohol and ether to give the title compound, white, fine crystals; m.p. 150—151.5° (cf. D-(threo)-isomer, m.p. 151.5—152°); $R_f$ = 0.48 (solvent *D*); $\nu_{max}$ (KBr): 3450 (OH), 3300 (NH), 1669 (C=O), 1583 (C=C), 1511 (NH); $^1$H NMR ($CDCl_3$-DMSO-$d_6$, 4:1, v/v) δ: 3.02 (s, 3H), 4.23—4.51 (m, 2H, $H_2$ and $H_3$), 4.60 (ddd, 1H, $J_3$,F = 40.3 Hz, $J_{3',2}$ = 7.2 Hz, $J_{3,3'}$ = 8.9 Hz), 5.03 (dd, 1H, $J_{1,OH}$ = 5.0 Hz, $J_{1,2}$ = 1.4 Hz), 5.91 (OH) (d, 1H, $J_{OH,1}$ = 5.0 Hz), 6.17 ($CHCl_2$) (s, 1H), 7.58 (d, 2H, 8.4 Hz), 8.19 (d, 2H, 8.5 Hz).

B. Dissolve the title compound of Example 7 (90 mg., 0.36 mmoles) in dry methanol (Mg. dried, 1.6 mL), triethylamine (0.1 mL) and methyl dichloroacetate (4 mL). Reflux the solution under nitrogen for 14 hrs. Evaporate solvent under vacuum to give a syrup. Chromatograph the syrup on a silica gel column, elute with ethyl acetate-hexanes (3:1, v/v) to give a solid after evaporation of the solvent (yield, 102 mg, 86.8%). Recrystallize the solid from isopropyl alcohol and ether to give the title compound as fine, white crystals, m.p. 148—149° and having identical ir and $^1$H NMR spectra with those, respectively, of the dichloroacetamido derivative prepared from the phthalimide in accordance with procedure A of Example 8.

Example 9

D,L-(*threo*)-1-(4-Methylsulfonylphenyl)-2-Amino-3-Fluoro-1-Propanol by resolution of D,L-(*threo*)1-(4-Methylsulfonylphenyl)-2-Amino-3-Fluoro-1-Propanol

A. *Resolution of (+)-(S)-O-methylmanclelic acid.* Heat 40.0 g (0.241 moles) of racemic (±)-α-phenylacetic acid [D. G. Neilson et al. *J. Chem. Soc.,* (1962), 1519] with 40.0 g (0.242 moles) of *d*-ephedrine (available from Aldrich) in 180 mL of 95% ethanol under reflux on a steam bath. Cool the resulting solution to room temperature slowly and leave undisturbed overnight (16 hrs). Filter the resulting crystallized solid and wash same with 95% ethanol (20 mL) and ethyl ether to give 35.6 g. Recrystallize (twice) the solid from 95% ethanol to give 26.5 g of salt of *d*-ephedrine and (+)-α-methoxy-α-phenylacetic acid [(+)-(*S*)-*O*-methylmandelic acid], m.p. 185—188°, $[\alpha]_D^{21}$ +72.8° (c, 4.64, MeOH). Acidify 26.3 g of the solid with 90 mL of ice-cooled sulfuric acid, with stirring to give a solution. Add sodium chloride (31 g) and stir the resulting mixture. Add 100 mL of dichloromethane to the mixture to give a voluminous precipitate (ephedrine, sulfuric acid salt). Add another 100 mL portion of dichloromethane to the mixture and filter the mixture through a glass filter. Wash the solid with 100 mL of dichloromethane. Shake the filtrate and separate the organic and aqueous layers. Extract the aqueous layer with 100 ml of dichloromethane. Dry the combined organic layers over anhydrous magnesium sulfate. Evaporate the solvent to give an oil which solidifies on cooling to yield 13.2 g of the title compound as a solid: m.p. 60.5—62.0°, $[\alpha]_D^{22}$ +149° (C, 5.61, MeOH).

B. Formation of seed crystals of the salt of (+)-(*S*)-*O*-Methylmandelic acid and *D*-(threo)-1-(4-Methylsulfonylphenyl)-2-Amino-3-Fluoro-1-Propanol

Dissolve (+)-(*S*)-*O*-Methylmandelic acid from Example 9, procedure A (44.9 mg, 0.270 mole) and authentic D-*threo*-1-(4-methanesulfonylphenyl)-2-amino-3-fluoro-1-propanol (obtained by hydrolysis of the corresponding 2-dichloroacetamido derivative prepared in accordance with USP 4,311,857 using 33% HCl solution followed by treatment with 30% NaOH solution and extraction of the free base) (66.9 mg, 0.270 mmole) in *n*-butanol (1.5 mL) by warming on a steam bath. Cool the solution slowly to room temperature and leave the cooled solution undisturbed for 15 hrs. Filter the crystalline solid by filtration and wash the solid with an ether-*n*-butanol mixture (1:1, v/v) 2 mL) and ether (yield 84 mg). Recrystallization gave fine needles of the title salt, m.p. 160—161.5°; $[\alpha]_D^{23}$ +22.7° (*c* 11.8, MeOH); $\nu_{max}$ (KBr): 3400, 3190, 2870, 2700, 2540, 1560, 1400, 1302 $cm^{-1}$.

C. Condition 1: Crystallizing the diastereomeric salt with stirring

Diss lve *D,L*-(threo)-1-(4-methylsulfonylphenyl)-2-amino-3-flu ro-1-propanol of Exampl 8 (1.193 g, 4.822 mm les) and (+)-(*S*)-*O*-methylmandelic acid (0.8012 g, 4.822 mmoles) f Example 9A in *n*-butanol (25 mL) by warming n a steam bath. Whil th resulting solution is c oling t room temperature, seed th warm solution with an authentic sampl of the salt (2 mg) described in proc dur (B) Example 9. Stir th

mixture rigorously for 2 hrs. at room temperature. Remove the precipitated solid by filtration and wash the solid with an ice-cooled (1:1, v/v) *n*-butanol-anhydrous ether mixture (10 mL) and anhydr us ether, and then dry same under vacuum (0.5 mm Hg) overnight, yield 0.8540 g; $[\alpha]_D^{21.2}$ +29.9° (*c* 8.36, MeOH). Recrystallize the partially resolved solid (0.8540 g) from *n*-butanol (7 mL) to afford a solid (0.4566 g), m.p. 155—158.5° (softened at 150°C), $[\alpha]_D^{23.5}$ +23.4° (*c* 7.72, MeOH).

Dissolve the salt (0.4566 g, 1.104 mmoles) in warm water (10 mL) and cool the resulting solution in an ice-water bath. Basify the cold solution by adding a 30% sodium hydroxide solution portionwise with stirring. Add sodium chloride (3 g) and chloroform (20 mL) and stir the mixture. Remove a precipitate (sodium salt of the acid) by filtration and wash same with chloroform. Shake the filtrate and separate the organic layer. Extract the aqueous layer with chloroform (3 × 20 mL). Dry the combined extracts over anhydrous sodium sulfate. Concentrate the solution concentrated to give a syrup and dissolve same in absolute ethanol 5 mL). Filter the solution through a cotton plug. Evaporate the solvent to give a syrup. Remove the last traces of solvent from the syrup under vacuum to give a D-(threo)-1-(4-methylsulfonylphenyl)-2-amino-3-fluoro-1-propanol as a crystalline solid yield 0.2643 g; $[\alpha]_D^{23}$ −33.6° (*c* 7.06, MeOH), m.p. 108.5—110.0°; optical purity %: −32.6°/−33.6° × 100 = 97.0%. The isolated free amine contained the D-(threo) enantiomer, the title compound, (98.5%) and the L-(threo) enantiomer (1.4%). The overall yield from the D,L-(threo)-1-(4-methylsulfanoylphenyl)-2-amino-3-fluoro-1-propanol was 0.264/0.569 = 44.1%.

D. Condition 2: Allowing crystallization of the diastereomeric salt to proceed without stirring

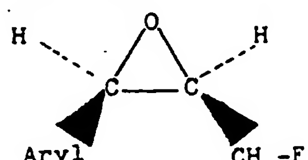
Dissolve the title compound of Example 8 (1.4308 g, 5.784 mmoles) and (+)-(*S*)-*O*-methylmandelic acid of Example 9A (0.9611 g, 0.0611 g) in hot *n*-butyl alcohol (20 mL) on a steam bath. Cool the solution to room temperature, and seed the turbid solution with the authentic salt described in procedure B of Example 9 and leave the seeded solution at room temperature without disturbance for 65 hrs. Collect the crystalline solid by filtration and wash the collected solid with an *n*-butanol and ether mixture (1:1, v/v) 10 mL) and ether (45 mL), and finally dry under vacuum, yield 1.4289 g; $[\alpha]_D^{21.9}$ +35.9° (*c* 9.03, MeOH). Recrystallize the partially enriched solid (1.375 g) from *n*-butanol (15 mL) as described above except leave same at room temperature for 24 hrs, yield 0.005 g; $[\alpha]_D^{22.4}$ +31.7° (*c* 8.80, MeOH).

Recrystallize this solid (0.9118 g) from *n*-butanol (10 mL) as described above to give a solid (yield 0.6951 g), $[\alpha]_D^{22.2}$ +28.3° (*c* 9.00, MeOH). Recrystallize this material (0.6349 g) from *n*-butanol (5 mL) to afford a solid (yield 0.5046 g). $[\alpha]_D^{23.8}$ +26.4° (*c* 10.3, MeOH). Recrystallize the major portion of this solid (0.4433 g) from *n*-butanol (4 mL) to give a solid (yield 0.2325 g), m.p. 159—161.5°, $[\alpha]_D^{23.0}$ +24.2° (*c* 9.95, MeOH). Decompose this salt (0.1800 g) using sodium hydroxide solution as described in procedure *B* of this Example and isolate the title compound (yield 0.1013 g, 94.1%); $[\alpha]_D^{23.0}$ −32° (*c* 1.95, MeOH) cf. authentic sample of the title compound of this Example, $[\alpha]_D^{22}$ −35° (*c* 2.03, MeOH). Optical purity %: −32°/−35° × 100 = 91%.

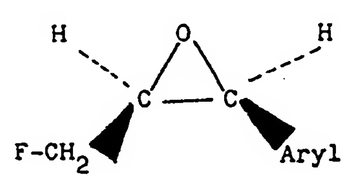
Racemic mixtures of the following D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanols may be prepared using the appropriate reagents and thereafter resolved by fractional crystallization of their diastereomeric salts with the appropriate optically active acid in accordance with the procedures detailed hereinabove as well as the prior teachings of S. H. Wilen, in "Topics in Stereochemistry" ed. by N. L. Allinger and E. L. Eliel, Vol. 6, p. 107 et seq., Wiley-Interscience, New York, 1971 and R. B. Woodward et al., *Tetrahedron*, Vol. 19 (1963) page 247 et seq.f.157

## Claims

1. A process for preparation of compounds represented by formulas IVa and IVb:

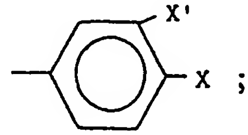


IVa



IVb

wherein Aryl is



and wherein each of X and X′ is independently $NO_2$, $SO_2R_1$, $SO_2NH_2$, $SO_2NHR_1$, $OR_1$, $R_1$, CN, halogen, hydrogen, phenyl, or phenyl substituted by 1—3 halogens, $NO_2$, $SO_2R_1$, $R_1$ or $OR_1$; and wh rein $R_1$ is low r

alkyl; which c mprises contacting a *cis*-1-Aryl-3-fluoro-1-propen with a peroxyacid to form the compounds r presented by the formulas IVa and IVb.

2. The process of claim 1 wherein Aryl is selected from 4-methylsulfonylphenyl, 4-nitr phenyl and 4-sulfonamidophenyl.

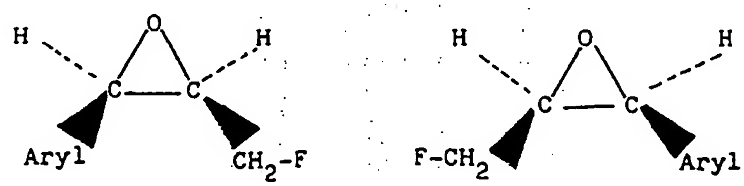
3. The process of claim 1 or 2 wherein the *cis*-1-Aryl-3-fluoro-1-propene is prepared by

a) contacting a 3-Aryl-2-propyn-1-ol with a fluorinating agent in an inert organic solvent to form 1-Aryl-3-fluoro-1-propyne; and

b) contacting the product of step (a) with a reagent selective for *cis*-hydrogenation

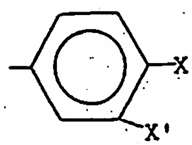
wherein Aryl is as defined in claim 1.

4. A compound represented by the formulas IVa and IVb:




IVa IVb

wherein Aryl is

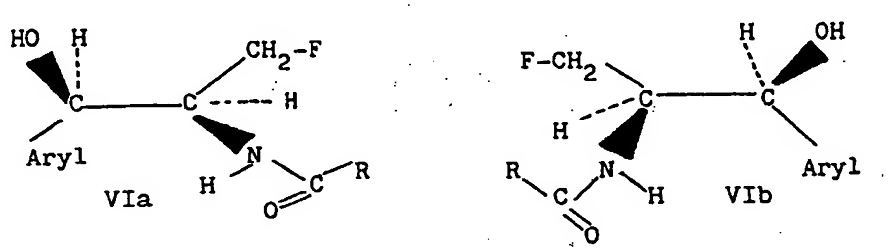



;

and wherein each of X and X' is independently $NO_2$, $SO_2R_1$, $SO_2NH_2$, $SO_2NHR_1$, $OR_1$, $R_1$, CN, halogen, hydrogen, phenyl or phenyl substituted by 1 to 3 halogens, $NO_2$, $SO_2R_1$, $R_1$ or $OR_1$; and wherein $R_1$ is lower alkyl.

5. The compound of claim 4 wherein Aryl is selected from 4-nitrophenyl, 4-sulfonamidophenyl and 4-methylsulfonylphenyl.

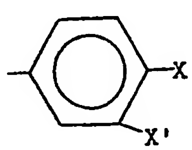
6. A process for the preparation of D,L-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanol represented by the formulas VIa and VIb:




VIa VIb

wherein R is lower alkyl or a halogenated derivative thereof, dihalogenodeuteriomethyl, 1-halogeno-1-deuterioethyl, 1,2-dihalogeno-1-deuterioethyl, azidomethyl and methylsulfonyl;

wherein Aryl is




;

and wherein each of X and X' is independently $NO_2$, $SO_2R_1$, $SO_2NH_2$, $SO_2NHR_1$, $OR_1$, $R_1$, CN, halogen, hydrogen, phenyl or phenyl substituted by 1 to 3 halogens, $NO_2$, $SO_2R_1$, $R_1$ or $OR_1$; and wherein $R_1$ is lower alkyl; which comprises the following steps:

(1) c nverting a *cis*-1-Aryl-2-(flu romethyl) xirane into D,L-(thre )-1-Aryl-2-amin -3-fluoro-1-pr pan l either by (i) contacting the *cis*-1-Aryl-2-(fluoromethyl)oxirane with an alkali metal azide to f rm D,L-(threo)-1-Aryl-2-azido-3-fluoro-1-propan l and then reducing the 2-azido group to the 2-amin group or (ii) c ntacting the *cis*-1-Aryl-2-(fluorom thyl) xiran with an imido compound to form a D,L-(threo)-1-Aryl-2-imido-3-fluoro-1-propanol and then converting the 2-imido group t a 2-amin group th reby forming D,L-(threo)-1-

Aryl-2-amino-3-fluoro-1-propanol;

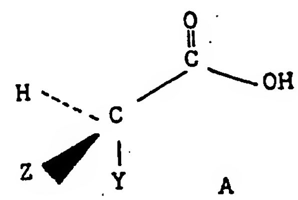
(2) contacting the product of step (1) with a lower alkanoic acid derivativ selected from lower alkyl alkan ic acid anhydrides, lower alkyl alkanoyl halides, a l w r alkyl hal geno alkanoic halide or anhydrid in the presence of base, or with lower alkyl ester of an α,α-dihalogeno acetic acid or of an α,α-dihalogeno propionic acid ester in a lower alkanol to produce the compounds of formulas VIa and VIb; and

(3) recovering the compounds of formulas VIa and VIb.

7. The process of claim 6 which further comprises recovering D-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol represented by formula Va from fractional crystallization of diastereomeric salts of compounds represented by formulas Va and Vb and an optically active acid; and thence performing step (2).

8. The process of claim 6 wherein Aryl is selected from 4-methylsulfonylphenyl, 4-nitrophenyl and 4-sulfonamidephenyl.

9. The process of claim 7 wherein the optically active acid has the structure represented by formula A:



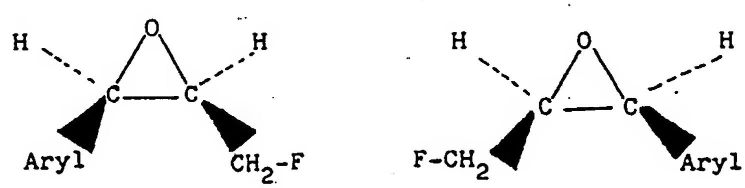
A

wherein Z is a bulky group and wherein Y is a polar group.

10. The process of claim 7 wherein Aryl is 4-methylsulfonylphenyl and wherein, in the optically active acid, Z is phenyl or naphthyl and Y is $(C_1$—$C_6)$alkyloxy.

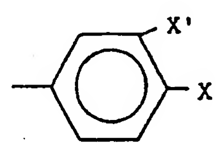
**Patentansprüche**

1. Verfahren zur Herstellung von Verbindungen der Formeln IVa und IVb



IVa IVb

worin Aryl




ist und worin X und X' jeweils unabhängig voneinander $NO_2$, $SO_2R_1$, $SO_2NH_2$, $SO_2NHR_1$, $OR_1$, $R_1$, CN, Halogen, Wasserstoff, Phenyl oder durch 1 bis 3 Halogene, $NO_2$, $SO_2R_1$, $R_1$ oder $OR_1$ substituiertes Phenyl sind und worin $R_1$ Niederalkyl ist, umfassend das In-Berührung-Bringen eines cis-1-Aryl-3-fluoro-1-propens mit einer Peroxysäure zur Bildung der durch die Formeln IVa und IVb dargestellten Verbindungen.

2. Verfahren nach Anspruch 1, worin Aryl aus 4-Methylsulfonylphenyl, 4-Nitrophenyl und 4-Sulfonamidophenyl ausgewählt ist.

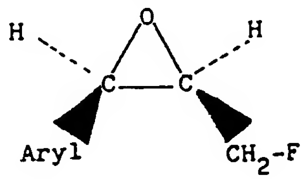
3. Verfahren nach Anspruch 1 oder 2, worin das cis-1-Aryl-3-fluoro-1-propen dadurch hergestellt wird, daß

a) ein 3-Aryl-2-propin-1-ol mit einem Fluorierungsmittel in einem inerten organischen Lösungsmittel in Berührung gebracht wird, wodurch 1-Aryl-3-fluoro-1-propin gebildet wird, und

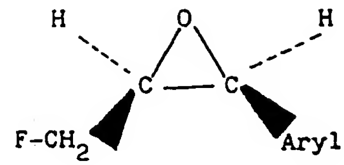
b) das Product aus Schritt (a) mit einem selektiv arbeitenden Reagens für die cis-Hydrierung in Berührung gebracht wird,

wobei Aryl di in Anspruch 1 angegebenen Bedeutungen hat.

4. Verbindung der Formeln IVa und IVb

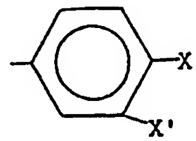


IVa



IVb

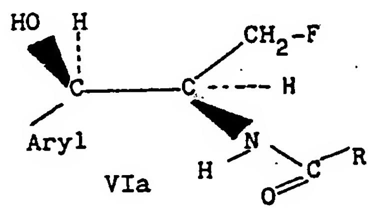
worin Aryl



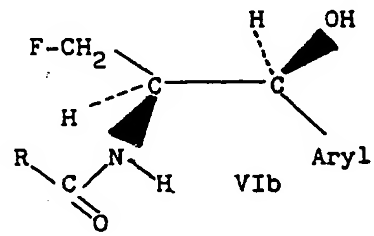
ist und worin X und X' jeweils unabhängig voneinander $NO_2$, $SO_2R_1$, $SO_2NH_2$, $SO_2NHR_1$, $OR_1$, $R_1$, CN, Halogen, Wasserstoff, Phenyl oder durch 1 bis 3 Halogene, $NO_2$, $SO_2R_1$, $R_1$ oder $OR_1$ substituiertes Phenyl sind und worin $R_1$ Niederalkyl ist.

5. Verbindung nach Anspruch 4, worin Aryl aus 4-Methylsulfonylphenyl, 4-Nitrophenyl und 4-Sulfonamidophenyl ausgewählt ist.

6. Verfahren zur Herstellung von D,L-(threo)-1-Aryl-2-acylamido-3-fluoro-1-propanol der Formeln VIa und VIb

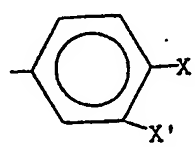


VIa



VIb

worin R Niederalkyl oder ein halogeniertes Derivat desselben, Dihalogenodeuteriomethyl, 1-Halogeno-1-deuterioethyl, 1,2-Dihalogeno-1-deuterioethyl, Azidomethyl und Methylsulfonyl ist, worin Aryl



ist und worin X und X' jeweils unabhängig voneinander $NO_2$, $SO_2R_1$, $SO_2NH_2$, $SO_2NHR_1$, $OR_1$, $R_1$, CN, Halogen, Wasserstoff, Phenyl oder durch 1 bis 3 Halogene, $NO_2$, $SO_2R_1$, $R_1$ oder $OR_1$ substituiertes Phenyl sind und worin $R_1$ Niederalkyl ist,

umfassend die folgenden Schritte:

(1) Umwandeln eines cis-1-Aryl-2-(fluoromethyl)oxirans in D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol entweder durch (i) In-Berührung-Bringen des cis-1-Aryl-2-(fluoromethyl)oxirans mit einem Alkalimetallazid, wodurch D,L-(threo)-1-Aryl-2-azido-3-fluoro-1-propanol gebildet wird, und anschließendes Reduzieren der 2-Azido-Gruppe in die 2-Amino-Gruppe oder (ii) In-Berührung-Bringen des cis-1-Aryl-2-(fluoromethyl)oxirans mit einer Imido-Verbindung, wodurch D,L-(threo)-1-Aryl-2-imido-3-fluoro-1-propanol gebildet wird, und anschließendes Umwandeln der 2-Imido-Gruppe in eine 2-Amino-Gruppe, wodurch D,L-(threo)-1-Aryl-2-amino-3-fluoro-1-propanol gebildet wird;

(2) In-Berührung-Bringen des Produkts aus Schritt (1) mit einem Derivat einer niederen Alkansäure, das aus Niederalkylalkansäureanhydriden, Niederalkylalkanoylhalogeniden, einem Niederalkylhalogenoalkansäurehalogenid oder -anhydrid ausgewählt ist, in Gegenwart einer Base oder mit einem Niederalkylester einer α,α-Dihal genoessigsäure oder eines α,α-Dihalogenpropionsäureest rs in ein m nieder n Alkanol zur H rstellung der Verbindungen d r Formeln VIa und VIb; und

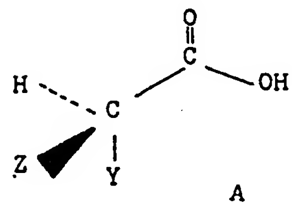
(3) Isolieren der V rbindungen d r Formeln VIa und VIb.

7. Verfahren nach Anspruch 6, weiterhin umfassend di Isoli rung von D-(thr o)-1-Aryl-2-amino-3-fluoro-1-propanol der Formel Va durch fraktionierte Kristallisation diast reomerer Salze der Verbindungen

der F rmeln Va und Vb und einer optisch aktiven Säure und die anschließende Durchführung des Schrittes (2).

8. Verfahren nach Anspruch 6, worin Aryl aus 4-Methylsulfonylphenyl, 4-Nitrophenyl und 4-Sulfonamidophenyl ausgewählt ist.

9. Verfahren nach Anspruch 7, worin die optisch aktive Säure die durch die Formel A



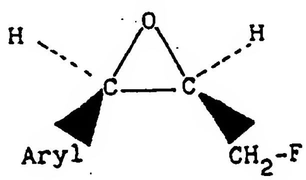
A

dargestellte Struktur hat, worin Z eine sperrige Gruppe ist und worin Y eine polare Gruppe ist.

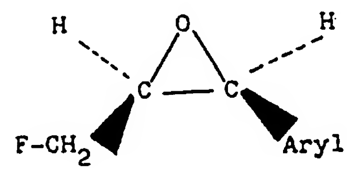
10. Verfahren nach Anspruch 7, worin Aryl 4-Methylsulfonylphenyl ist und worin in der optisch aktiven Säure Z Phenyl oder Naphthyl ist und Y ($C_1$—$C_6$)-Alkyloxy ist.

## Revendications

1. Procédé de préparation de composés représentés par les formules IVa et IVb:

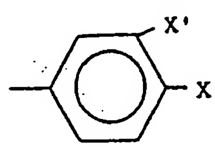


IVa



IVb

dans lesquelles aryl est



;

et dans lesquelles X et X' sont chacun indépendemment $NO_2$, $SO_2R_1$, $SO_2NH_2$, $SO_2NHR_1$, $OR_1$, $R_1$, CN, halogène, hydrogène, phényle ou phényle substitué par 1 à 3 halogènes, $NO_2$, $SO_2R_1$, $R_1$ ou $OR_1$; et dans lesquelles $R_1$ est un alkyle inférieur; qui comprend la mise en contact d'un *cis*-1-Aryl-3-fluoro-1-propene avec un peroxyacide pour former les composés représentés par les formules IVa et IVb.

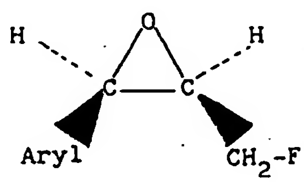
2. Procédé selon la revendication 1 dans lequel aryl est choisi parmi 4-méthylsulfonylphényle, 4-nitrophényle et 4-sulfonamidophényle.

3. Procédé selon la revendication 1 ou 2 dans lequel le *cis*-1-aryl-3-fluoro-1-propène est préparé par

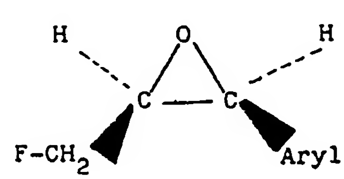
a) la mise en contact d'un 3-aryl-2-propyne-1-ol avec un agent fluorant dans un solvant organique inerte pour former le 1-aryl-3-fluoro-1-propyne; et

b) la mise en contact du produit de l'étape a) avec un réactif sélectif pour la *cis*-hydrogénation, Aryl étant tel que défini dans la revendication 1.

4. Composé représenté par les formules IVa et IVb:

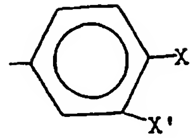


IVa



IVb

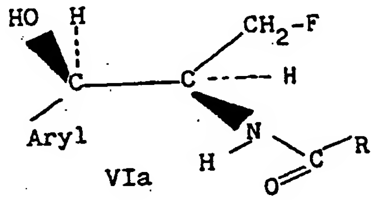
dans lesquelles aryl est



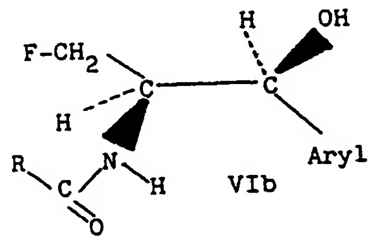
et dans lesquelles X et X' sont chacun indépendemment $NO_2$, $SO_2R_1$, $SO_2NH_2$, $SO_2NHR_1$, $OR_1$, $R_1$, CN, halogène, hydrogène, phényle ou phényle substitué par 1 à 3 halogènes, $NO_2$, $SO_2R_1$, $R_1$ ou $OR_1$; et dans lesquelles $R_1$ est un alkyle inférieur.

5. Composé selon la revendication 4 dans lequel aryl est choisi parmi 4-nitrophényle, 4-sulfonamidophényle et 4-méthylsulfonylphényle.

6. Procédé pour la préparation du D,L-(thréo)-1-aryl-2-acylamido-3-fluoro-1-propanol représenté par les formules VIa et VIb:

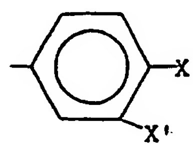


VIa



VIb

dans lesquelles R est un alkyle inférieur ou un dérivé halogéné de celui-ci, un groupe dihalogénodeuteriométhyle, 1-halogéno-1-deuterioéthyle, 1,2-dihalogéno-1-deutérioéthyle, azidométhyle et méthyl sulfonyle; dans lesquelles aryl est

 ;

et dans lesquelles X et X' sont chacun indépendemment $NO_2$, $SO_2R_1$, $SO_2NH_2$, $SO_2NHR_1$, $OR_1$, $R_1$, CN, halogène, hydrogène phényle ou phényle substitué par 1 à 3 halogènes, $NO_2$, $SO_2R_1$, $R_1$ ou $OR_1$; et dans lesquelles $R_1$ est un alkyle inférieur; qui comprend les étapes suivantes:

(1) conversion d'un *cis*-1-aryl-2-(fluorométhyle) oxirane en D,L-(thréo)-1-aryl-2-amino-3-fluoro-1-propanol soit par (i) mise en contact du *cis*-1-aryl-2-(fluorométhyle)oxirane avec un azothydrure de métal alcalin pour former le D,L-(thréo)-1-aryl-2-azido-3-fluoro-1-propanol puis réduction du groupe 2-azido en le groupe 2-amino ou (ii) mise en contact du *cis*-1-aryl-2-(fluorométhyle)oxirane avec un composé imido pour former un D,L-(thréo)-1-aryl-2-imido-3-fluoro-1-propanol puis conversion du groupe 2-imido en un groupe 2-amino formant ainsi le D,L-(thréo)-1-aryl-2-amino-3-fluoro-1-propanol;

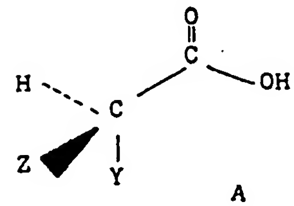
(2) mise en contact du produit de l'étape (1) avec un dérivé d'acide alcanoique inférieur choisi parmi les alkyl anhydrides d'acides alcanoiques, les alkyl halogénures d'alcanoyle inférieurs, un alkyl halogénure ou anhydride halogénoalcanoique inférieur en présence d'une base, ou avec un alkyl ester inférieur d'un acide alpha, alpha-dihalogénoacétique ou d'un ester d'acide alpha, alpha-dihalogénopropionique dans un alcanol inférieur pour produire les composés des formules VIa et VIb; et

(3) récupération des composés des formules VIa et VIb.

7. Procédé selon la revendication 6 qui comprend en outre la récupération du D-(thréo)-1-aryl-2-amino-3-fluoro-1-propanol représenté par la formule Va par cristallisation fractionnée des sels diastéréomères des composés représentés par les formules Va et Vb et d'un acide optiquement actif; puis la réalisation de l'étape (2).

8. Procédé selon la revendication 6 dans lequel aryl est choisi parmi 4-méthylsulfonylphényle, 4-nitrophényle et 4-sulfolamidophényle.

9. Procédé selon la revendication 7 dans lequel l'acide optiquement actif a la structure représentée par la formule A:



A

dans laquelle Z est un groupe volumineux et dans laquelle Y est un groupe polaire.

10. Procédé selon la revendication 7 dans lequel aryl est 4-méthylsulfonylphényle et dans lequel, dans l'acide optiquement actif, Z est phényle ou naphtyle et Y est alkyloxy en $C_1$—$C_8$.